

CLINICAL PRACTICE

Perioperative use of oxygen: variabilities across age

W. Habre^{1,2*} and F. Peták^{2,3}

¹ Geneva Children's Hospital, University Hospitals of Geneva, 6 rue Willy Donzé, CH-1205 Geneva, Switzerland

² Pathophysiological Experimental Platform, Department of Anaesthesiology, Pharmacology and Intensive Care, University of Geneva, 1 rue Michel Servet, CH-1205 Geneva, Switzerland

³ Department of Medical Physics and Informatics, University of Szeged, 9 Koranyi fasor, H-6720 Szeged, Hungary

* Corresponding author. E-mail: walid.habre@hcuge.ch

Editor's key points

- Oxygen supplementation is a key therapy in anaesthesia and intensive care, but recent evidence points to detrimental effects.
- Hyperoxia enhances oxidative injury by increasing reactive oxygen metabolites, with effects on the pulmonary, cardiovascular, immune, and nervous systems.
- The potentially detrimental effects of hyperoxia are more pronounced at the extremes of age.

Enormous interest has emerged in the perioperative use of high concentrations of inspired oxygen in an attempt to increase tissue oxygenation and thereby improve postoperative outcome. An extensive debate has arisen regarding the risk/benefit ratio of oxygen therapy, with some researchers advocating the benefits of perioperative hyperoxia, particularly with regard to surgical site infection, whereas others emphasize its detrimental consequences on multiple organs, particularly the lungs and the brain. As one aspect of this debate, there is increased awareness of effects of reactive oxygen metabolites, a feature that contributes to the complexity of achieving consensus regarding optimum oxygen concentration in the perioperative period. Many reviews have discussed the pros and cons in the use of perioperative oxygen supplementation, but the potential importance of age-related factors in hyperoxia has not been addressed. The present narrative review provides a comprehensive overview of the physiological mechanisms and clinical outcomes across the age range from neonates to the elderly. Risks greatly outweigh the benefits of hyperoxia both in the very young, where growth and development are the hallmarks, and in the elderly, where ageing increases sensitivity to oxidative stress. Conversely, in middle age, benefits of short-term administration of perioperative oxygen therapy exceed potential adverse change effects, and thus, oxygen supplementation can be considered an important therapy to improve anaesthesia management.

Keywords: atelectasis; hyperoxia; oxidative stress; oxygenases/toxicity surgical site infection

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After its initial discovery as a 'fire air' in 1771 by Carl Wilhelm Scheele, and the activities of Antoine Lavoisier leading to worldwide recognition of its value,¹ the use of oxygen (O₂) in medical practice spread throughout the 19th century. Today, not a single anaesthetic procedure is performed without consideration of O₂ as an important component of management. The usefulness and benefits of O₂ administration remained unchallenged until a few decades ago when our understanding of oxidative stress and O₂ toxicity became more comprehensive, and a more balanced and pragmatic application of O₂ therapy was proposed. In recent years, a growing debate has emerged regarding the benefits and risks involved in the perioperative use of high concentrations of inspired O₂, with physiologists and pharmacologists emphasizing the toxicity of this gas, while anaesthetists and intensivists rather stress the importance of O₂ in improving patient care through decreasing morbidity.

A number of systematic reviews and meta-analyses provide evidence of the risks/benefits of O₂ at various concentrations and for different durations of administration, but the lack of

clear-cut conclusions leads to confusion and the absence of evidence-based guidelines for use in routine anaesthesia practice. This discrepancy in the scientific literature is mainly attributable to the multifactorial facets of perioperative care, with O₂ being one limb of the highly complex decision-making network for individualized anaesthesia management of patients who demonstrate enormous inter-individual differences. Accordingly, anaesthetists require a critical appraisal of the results of recent studies, describing factors that affect the efficacy of O₂ therapy. Such factors are either patient-related (age, genetics, gender, environment, etc.) or depend on the type and context of the procedure and on the perioperative management by the anaesthetist. The present unsystematic narrative review highlights recent advances in the perioperative use of O₂ with a critical analysis of its advantages and disadvantages, and attempts to define the use of O₂ at different concentrations, based on the dual characteristics of O₂ during anaesthesia. A thorough and comprehensive literature search in medical databases (PubMed, Web of Science, and

Google Scholar) was performed with stepwise changes in relevant keywords focusing on each topic of interest addressed in the current review. A critical literature review was made with an objective of providing a balanced evaluation of all aspects of the topic discussed. Nevertheless, as a result of the extremely broad spectrum of publications related to perioperative oxygen use, unintentional bias caused by omission of potentially relevant articles cannot be fully excluded. However, recommendations are based on the most recent original research and meta-analyses currently available.

Oxygen as a carrier gas in anaesthesia practice

The use of O₂ as a vehicle for volatile anaesthetic agents goes back to nitrous oxide (N₂O) inhalation anaesthesia by Edmund Andrews in 1868 and the use of ether-based anaesthesia by Arno Luckhardt in 1918.¹ In these pioneering achievements, O₂ concentration was kept in the range of that in room air. Subsequent more thorough understanding of the adverse consequences of anaesthesia and surgical procedures on pulmonary physiology and awareness of difficult airway management with the potential risk of hypoxaemia led to the recognition that elevated inspired O₂ concentration is beneficial in maintaining optimum gas exchange. Accordingly, early guidelines for anaesthesia practice emphasized the important role of pre-oxygenation with 100% O₂ before i.v. induction, with the subsequent maintenance of relatively high concentrations (40–50%).² The use of such concentrations stems from the identification of hypoxaemia as a major risk factor accompanied by increased perioperative morbidity and mortality.^{3, 4} Moreover, administration of high concentrations of O₂ does not cause major alterations in the flow dynamics in the airways, despite the density and viscosity of O₂ being greater than those of nitrogen by about 20 and 10%, respectively.⁵ While these physical characteristics have negligible effects in routine clinical practice, such differences can have major impacts on turbulent flow in the conducting airways and can bias the respiratory mechanical outcome systematically.⁶

Metabolic and immunological aspects

One of the major sources of variability in the established use of O₂ concentration in anaesthesia practice is related to the dual nature of this gas, with its beneficial profile in treating hypoxaemia and its deleterious potential for adverse metabolic and immunological alterations. The normal oxidative metabolism of cells, controlled by the cytochrome oxidase system in mitochondria, generates free electrons that are captured by oxygen.^{7, 8} Incomplete reduction of O₂ leads to reactive oxygen metabolites (ROMs), which include superoxide and hydroxyl radicals, and also hydrogen peroxide. The oxidative stress resulting from these ROMs is a primary cause of DNA damage, impairment of mitochondrial function and organ injuries affecting primarily the brain and lung parenchyma.^{8, 9} While this generalized damage is encountered in patients of all types, clinical manifestations are greatly affected by a number of factors including the concentration and duration

of exposure and age. The latter factor is of particular importance, as the developing organs are highly prone to damage by ROMs.⁸ While the presence of this mechanism explains the concern in applying elevated concentrations of O₂, anaesthetists must make a distinction between different age groups when anaesthesia management requires use of a high O₂ concentration.

In addition to the tissue injury induced by ROMs, these chemically reactive molecules exert a dual effect on the immune system. ROMs are involved in bactericidal host defence mechanisms. Reduced nicotinamide adenine dinucleotide phosphate oxidase¹⁰ located in the membrane of phagocytic vesicles, catalyses formation of superoxide in an oxygen-dependent process. This superoxide is reduced to hydrogen peroxide, which then combines with chloride to form bacteriotoxic hypochlorous acid in the myeloperoxidase reaction.¹¹ In addition, supplemental high O₂ concentration can enhance the gene expression of pro-inflammatory cytokines in the lungs both *in vivo*¹² and *in vitro*.¹³ These phenomena lead to improved alveolar macrophage function.¹² On the other hand, the effects of hyperoxia on actin cause endothelial cell damage¹⁴ and impair antibacterial function of macrophages.¹⁵ This effect must be considered in the context of general anaesthesia, which has a well-characterized suppressive effect on numerous immunological parameters including phagocytosis and the alveolar macrophage function.^{12, 16, 17} As a result of these opposing effects on the immune system, there is no evidence of additional adverse net effects of high concentrations of O₂ on the depressed immunological function observed during anaesthesia.

Physiological aspects

Ventilatory effects

It is well established that general anaesthesia promotes ventilation heterogeneity through a disturbance of the equilibrium between the expanding thoracic and retracting pulmonary forces.¹⁸ Various pathophysiological and pharmacological factors contribute to this adverse alteration in the respiratory system. Respiratory depression by anaesthetic agents, use of neuromuscular blocking agents, body position of the patient, type of surgical procedure, age, obesity, and inhibition of hypoxic pulmonary vasoconstriction are among the major factors.^{18, 19} The use of high concentrations of O₂ further enhances ventilation defects by inducing airway closure and alveolar collapse.²⁰ This mechanism is related to the increased gradient between intra-alveolar partial pressure of O₂ and mixed venous blood in the capillaries. This results in rapid diffusion of O₂ across the alveolar-capillary barrier, subsequently leading to loss in alveolar distending pressure and hence alveolar collapse.^{21–23} The kinetics of such O₂-absorption atelectasis development is primarily determined by alveolar concentration of O₂ and time of administration. A number of previous studies involving the use of lung imaging techniques have established the existence of a threshold inspired fraction of O₂ (F_{I,O₂}), provided at the induction of anaesthesia until no clinically significant areas of alveolar derecruitment remain.^{20, 24, 25} Exceeding the critical threshold of F_{I,O₂} of 80%, leads to the rapid (within minutes) development of alveolar

collapse.^{20–22} Lung imaging studies have revealed that alveolar collapse persists despite application of recruitment manoeuvres when a high concentration of O₂ is maintained during anaesthesia.²⁴

In contrast to the consensus regarding the lung peripheral effects of acute hyperoxia, conflicting data have been reported as to how increased O₂ tension affects airway properties. One experimental investigation suggested that acute hyperoxia may have bronchodilatory potential by inhibiting cholinergically induced bronchoconstriction and potentiating bronchodilatory responses.²⁶ However, this beneficial effect was not consistently confirmed in subsequent investigations: some reports reinforced this finding,²⁷ while others indicated no benefit,²⁸ or even constriction of peripheral airways.²⁹ While further studies are necessary to resolve this controversy, results of recent studies have yielded increasing evidence of particular risks of supplemental O₂ in prematurity, because of its detrimental effects on airway smooth muscle, with possible development of bronchial hyperreactivity, and wheezing.^{30–31} This points again to the importance of patient age when risk/benefit ratio is considered for perioperative administration of O₂.

Circulatory effects

Perioperative hyperoxia exerts differential effects on the systemic and pulmonary circulations. Short-term application of hyperoxia decreases pulmonary vascular resistance, leading to increased blood volume with redistribution of regional pulmonary perfusion.³² This effect is beneficial in the event of enhanced ventilation-perfusion (V/Q) mismatch, as improvement in pulmonary perfusion can increase the net surface area available for pulmonary gas exchange. This phenomenon is of particular importance in hypoxaemic patients because of the low V/Q ratio.³³ Conversely, hyperoxia exerts a vasoconstrictive effect on the systemic arteries, which demands particular attention in the management of patients with pre-existing high systemic vascular resistance and impaired coronary circulation.^{34–35} This increase in systemic vascular resistance, which depends on O₂ concentration, leads to a decrease in cardiac output via both increased afterload and decreased preload.^{36–37} As a consequence of these cardiovascular alterations, hyperoxygenation can reduce tissue perfusion and compromise O₂ transport. The cerebral vasoconstrictive potential of hyperoxia is also of concern in the two age extremes where reductions in cerebral blood flow (CBF) can have significant deleterious consequences both on the immature³⁸ and aged brain.³⁹

Oxygen transport

There is a general misbelief among clinicians that elevation of F_IO₂ results in increased O₂ transport capacity, thereby improving oxygenation at the level of the microcirculation. However, as haemoglobin is fully saturated under physiological conditions, an increase in the arterial partial pressure of O₂ (P_aO₂) increases O₂ content of the blood only marginally.⁴⁰ In contrast, the presence of optimal cardiac output and mild hypercapnic vasodilation has a much greater impact in improving tissue oxygenation.⁴¹ As described, hyperoxia induces vasoconstriction

and decreases the blood flow in the microcirculation even in the presence of anaemia.⁴² Accordingly, high concentrations of O₂ can compromise tissue oxygenation rather than providing the anticipated beneficial effect.⁴³

Age-related aspects of perioperative oxygen delivery

Oxygen use in newborns and infants

One of the major dogmas concerning the use of hyperoxia fell from favour completely after the compelling evidence of the risks of using hyperoxia during neonatal resuscitation.⁴⁴ In premature and newborn infants, perioperative use of a high concentration of O₂ is of major concern. The resulting oxidative stress is responsible for major injuries, with the developing lungs and the brain of particular concern. Regarding the adverse pulmonary effects of hyperoxia, development of bronchopulmonary dysplasia (BPD) is the most important consequence.^{45–47} The high sensitivity of immature airway smooth muscle to even short periods of clinically moderate levels of O₂ (<60%) was recently demonstrated.³⁰ Further increase in O₂ concentration has been shown to lead to apoptosis, causing adverse structural and functional pulmonary alterations.³¹ O₂ and the consequent liberation of ROMs modify macromolecules such as DNA and proteins, inducing epithelial and endothelial cell injury, and thereby affecting airway structure and lung parenchymal compartments.^{48–50} All these adverse changes influence epithelial tight junctions, with a subsequent increase in alveolar-capillary barrier permeability leading to pulmonary oedema and induction of the inflammatory cascade,⁵¹ followed by development of bronchial hyperreactivity.^{52–53} The chronic presence of these pathophysiological changes can lead to airway and vascular remodeling in the lungs, with subsequent pulmonary hypertension,^{54–57} fibrosis, and development of BPD.^{53–58}

Evidence has accumulated of the role of decreased nitric oxide (NO) production in hyperoxia-induced lung injury with subsequent imbalance in the relaxation-constrictive regulation of the smooth muscle and lung parenchymal destruction.^{59–61} NO also affects lung structural development, including alveolarization,⁶² and is involved as a mediator of non-adrenergic, non-cholinergic signalling in the pathogenesis of the inflammatory response and in regulation of the pulmonary circulation.⁶³ These functions are inactivated in a hyperoxic environment,⁶⁴ which compromises NO effects and dependent pathways by increasing the activity of guanosine 3', 5'-cyclic monophosphate-dependent phosphodiesterases (c-GMP), resulting in impaired airway relaxation⁶⁵ and abnormal angiogenesis.^{65–66}

Titration inspired oxygen fraction is not straightforward in premature and term newborns. Indeed, because of the high affinity of fetal haemoglobin to O₂ and the shape of the O₂-haemoglobin dissociation curve, O₂ saturation (S_aO₂) over 92% might not accurately correlate with P_aO₂.⁶⁷ Small variations of oxygen saturation can indicate large variations of P_aO₂.⁶⁸ Nevertheless, targeting a S_aO₂ between 85 and 89% rather than 91 and 95% in premature infants was associated with a higher incidence of death before discharge, while maintaining higher S_aO₂ conferred a survival benefit, but at

the additional cost of an increased rate of severe retinopathy. Caution is therefore required when titrating O_2 perioperatively for preterm and low birth weight neonates, for whom hyperoxia can be particularly harmful, and the saturation of O_2 in the arterial blood (Sa_{O_2}) should be maintained between 88 and 94%.⁶⁹

Neonates with congenital heart disease (CHD) are another specific group where O_2 supplementation should be considered with great care and where O_2 therapy is challenging.⁷⁰ In acyanotic congenital heart disease (e.g. atrial or ventricular septal defects), the provision of a high concentration of O_2 can lead to a significant increase in systemic vascular resistance, with subsequent decreases in cardiac output and O_2 transport.⁷¹ By increasing pulmonary blood flow and causing an imbalance of the pulmonary to systemic perfusion, O_2 can precipitate circulatory instability in the presence of single ventricle physiology.⁷² Furthermore, in ductus-dependent CHD, O_2 therapy can jeopardize patency of the ductus arteriosus despite administration of prostaglandin, and there is therefore a consensus to maintain Sa_{O_2} between 75 and 85%.⁷⁰ In view of the regional differences in tissue oxygenation during cardiopulmonary bypass in children with congenital heart disease,⁷³ caution with O_2 is also mandatory after weaning from the bypass, and should be guided by the level venous saturation in O_2 (Sv_{O_2}) and regional oxygenation, monitored by near-infrared spectroscopy.

Intraoperative hypoxaemia in children is probably the most frequent complication in anaesthesia. Whereas delivery of high $F_{I_{O_2}}$ forms part of the first-line strategy in the presence of hypoxia (after airway obstruction, laryngospasm, or bronchospasm) or O_2 diffusion impairment (pulmonary oedema, surfactant depletion, or fibrosis), intraoperative O_2 concentration strategy differs completely when it comes to the prevention of hypoxaemia resulting from V/Q mismatch. The physiological characteristics of the infant respiratory system, with a highly compliant chest and increased lung elastic recoil, result in a loss in balance between chest-extending and lung-collapsing forces.⁷⁴ These features lead to a decrease in functional residual capacity, with a higher tendency to airway collapse, loss in lung volume and subsequent hypoxaemia. As a consequence, infants and pre-school children exhibit reduced tolerance to apnoea and gain little benefit from preoxygenation before the induction of anaesthesia.⁷⁵ Although no randomized clinical trials have addressed the advantages of gentle facemask ventilation during rapid sequence induction to prevent hypoxaemia,⁷⁶ such ventilation strategies at induction are now an integral part of good clinical practice guidelines.⁷⁷ Furthermore, as discussed above in connection with the physiological effects of hyperoxia, use of 100% $F_{I_{O_2}}$ during induction and maintenance of anaesthesia can further precipitate airway closure, with a significant decrease in lung volume participating in gas exchange.⁷⁸ As a V/Q mismatch in children is mainly attributable to a lung volume loss, the maintenance of anaesthesia with a high $F_{I_{O_2}}$ can mask the occurrence of atelectasis through a correction of the hypoxaemia related to the V/Q mismatch, with the preservation of high Sa_{O_2} .⁷⁴ Hence, it is good clinical practice to maintain $F_{I_{O_2}} \sim 30\text{--}35\%$ during anaesthesia maintenance in children in order to detect onset of intra-operative alveolar closure.

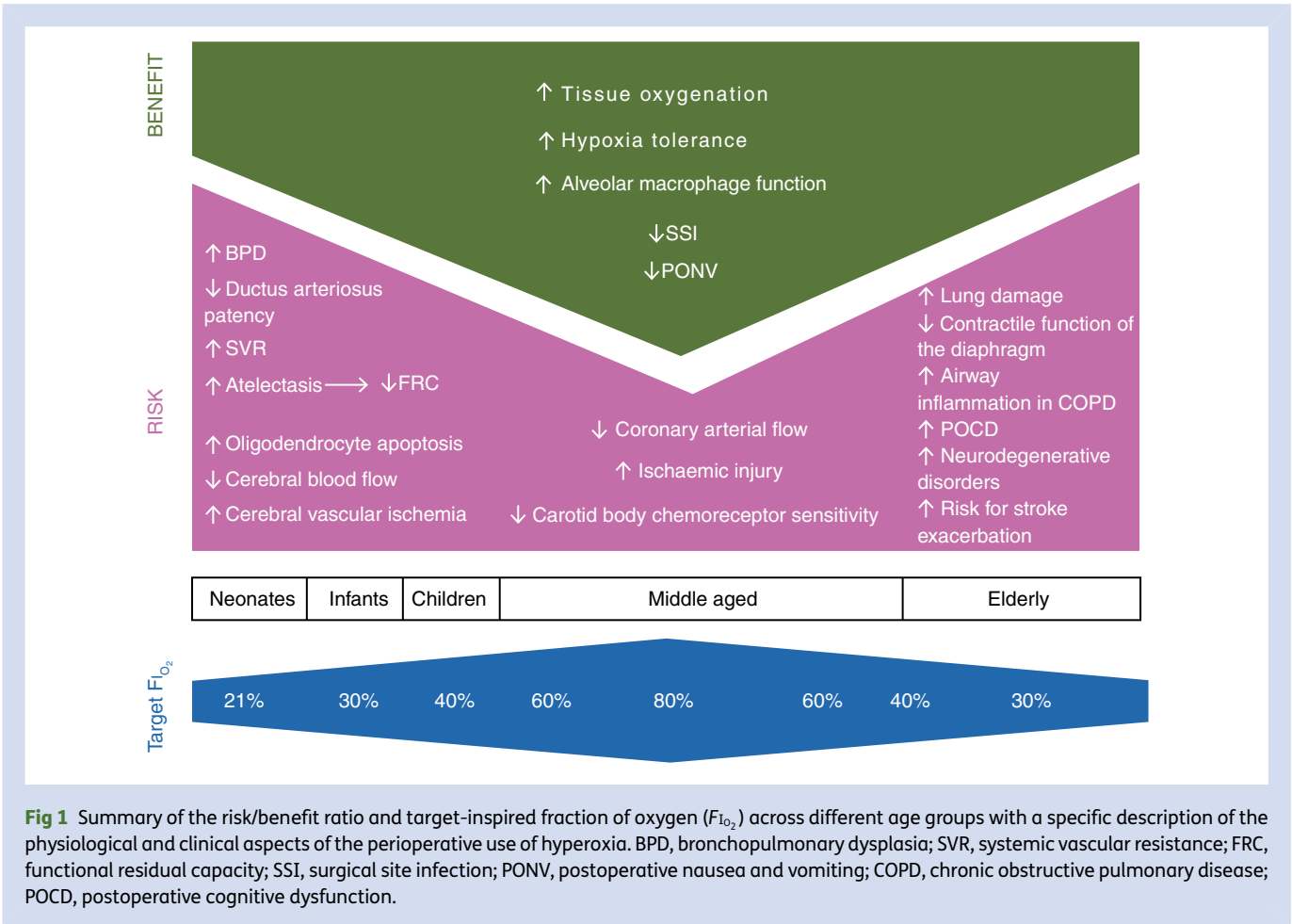
Increasing evidence has emerged from experimental studies on the harmful effects of postnatal hyperoxia on immature brain white matter.^{79–81} Hyperoxia and resulting ROMs lead to enhancement of inflammation and to oligodendrocyte apoptosis.⁸⁰ Furthermore, increase in cerebral vascular resistance and subsequent decrease in CBF add to the deleterious influence of hyperoxia in the immature brain.³⁸

These effects on the cerebral vasculature have to be taken into account in routine clinical practice, where perioperative ventilation with high concentrations of O_2 is often performed in an arbitrary manner in the context of traumatic brain injury or post resuscitation. The frequently associated hypocapnia attributable to mechanical ventilation or to the enhanced ventilation induced by O_2 delivery⁸² enhances cerebral vasoconstriction.³⁸ Moreover, administration of high concentrations of O_2 can intensify cerebral vascular ischaemia by inducing adverse autonomic and hormonal changes in several rostral brain regions.⁸³ Carbon dioxide (CO_2) is most effective in modulating the response to hyperoxia, with hypercapnia counteracting the vasoconstriction mediated by hyperoxia,⁸³ and hypocapnia worsening the effects of hyperoxia.³⁸

Oxygen use in middle aged

The last decade has seen a debate in the literature regarding the potential advantages of delivering high concentrations of O_2 intraoperatively.^{84–94} This abundant literature on the potential beneficial effects of perioperative high $F_{I_{O_2}}$ has led to several meta-analyses on the same topic.^{95–102} Many of these meta-analyses have important limitations with some failing to include negative trials⁸⁸ and others taking into consideration the data extracted from unpublished abstracts.¹⁰¹ Thus, a more nuanced presentation of their findings and conclusions is warranted. The controversy revolves around the efficacy of high perioperative O_2 supplementation in decreasing surgical site infection (SSI), postoperative nausea and vomiting (PONV), and ultimately morbidity and mortality.

The body of evidence for efficacy of high $F_{I_{O_2}}$ in reducing SSI is strengthened by an additional randomized controlled trial considered in the latest meta-analysis.¹⁰² The valuable effect of O_2 on surgical wounds stems from a potential increase in O_2 tissue delivery and hence prevention of tissue hypoxia, which otherwise promotes SSI.¹⁰³ A recent *in vitro* study demonstrated that while exposure to 80% $F_{I_{O_2}}$ led to increased levels of ROMs, the phagocytic activity of neutrophils and cytokine release were not affected.¹³ Hence, the main factor in the prevention of SSI seems to be related to the O_2 distribution to the surgical wounds rather than to O_2 content *per se*. Numerous perioperative factors jeopardize tissue blood flow and O_2 delivery such as the surgical trauma, hypothermia, hypovolaemia, oedema, severe anaemia, pain, a decreased cardiac output, or all.¹⁰⁴ Therefore, as pointed out by several authors, an increase in $F_{I_{O_2}}$ alone has no impact on wound O_2 levels in the presence of vasoconstriction. Besides haemodynamic optimization, the use of prophylactic antibiotics and decontamination of the digestive tract are also regarded as major players in reducing SSI and improving outcome.^{102 104 105} Perioperative use of high concentrations of O_2 should therefore be

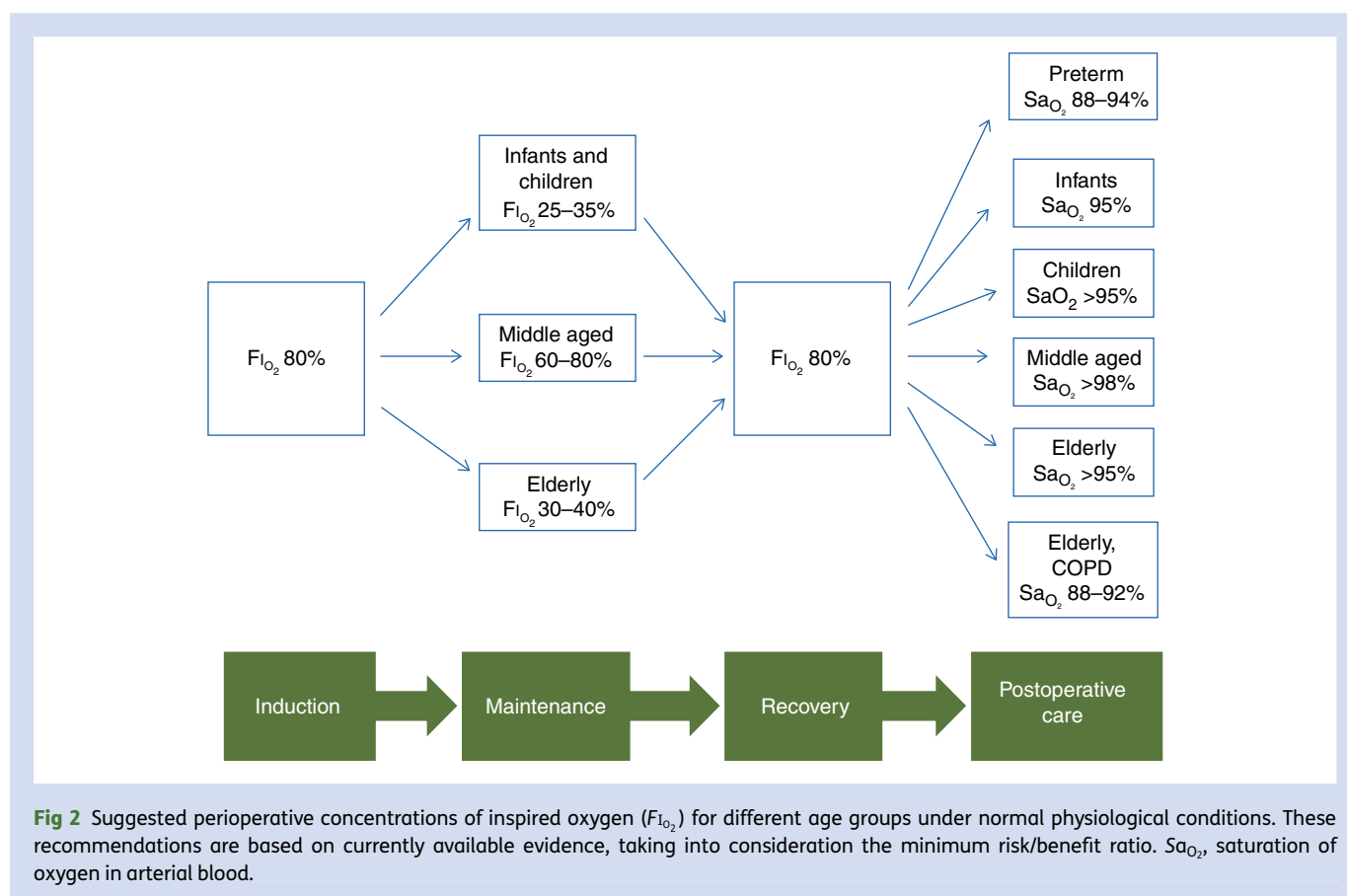


considered a supplemental strategy rather than an independent variable for reducing SSI, given that the efficacy of O_2 appears to be comparable with that of antibiotic prophylaxis in many surgical settings.¹⁰² In addition, subgroup analysis of large trials has failed to detect a benefit of high-inspired $F_{I_{O_2}}$ in some patients such as these with obesity.¹⁰⁶

Early investigations suggested that perioperative administration of a high $F_{I_{O_2}}$ for patients undergoing colorectal surgery significantly decreases the incidence of PONV by reducing intestinal hypoxaemia.¹⁰⁷ This was thought to be a plausible hypothesis as perioperative supplemental O_2 did not reduce PONV after other surgeries.^{108 109} However, as in the case of SSI, numerous factors contribute to PONV. These factors include surgical-dependent (duration and type of surgery, and gastroparesis), anaesthesia-dependent (inhalation agents, N_2O , long-acting opioids, and decreased perioperative fluids), or patient-related (age, gender, obesity, anxiety, history of motion sickness, or previous PONV).¹¹⁰ It is therefore hazardous to conclude that high $F_{I_{O_2}}$ decreases the incidence of PONV. The results of randomized controlled studies on this topic are not clear-cut.^{98 99} Not surprisingly, the most recent meta-analysis failed to provide strong evidence of a beneficial effect of high $F_{I_{O_2}}$ in preventing the occurrence of PONV.¹⁰² The prophylactic effect of a high $F_{I_{O_2}}$ was weak, with a benefit observed in only 1 of 15 patients

compared with normal $F_{I_{O_2}}$, which is inferior to effective antiemetic regimens.

The potential cardiovascular effects of hyperoxia are of concern in patients with a history of acute myocardial infarction, systemic arterial hypertension, or both. In the former, a recent meta-analysis failed to demonstrate usefulness of high concentrations of O_2 . This lack of efficacy (even a potentially harmful effect) of hyperoxia has been attributed to decreased coronary arterial flow and increased systemic vascular resistance.^{34 37 111} Moreover, ROMs can cause lipid peroxidation in the course of perioperative myocardial ischaemia-reperfusion, and further increase ischaemic injury.¹¹² This ROM-mediated reperfusion myocardial injury indicates the need for caution in the use of hyperoxia during and immediately after cardiopulmonary bypass, despite the potential benefit in reducing gas microemboli that develop during extracorporeal circulation.^{113 114} Hypertensive patients exhibit a biphasic arterial pressure response when exposed to 100% O_2 for 20 min, with an initial drop in systemic vascular resistance (and subsequently in systolic, diastolic, and mean arterial pressure) followed by an increase that diminishes cardiac output.¹¹⁵ This effect seems to be related to deactivation of carotid body chemoreceptors by hyperoxia. Hence, perioperative use of hyperoxia should be considered with particular care in



hypertensive patients, in those at a high risk of myocardial ischaemia, or both, two known risk factors that increase cardiovascular complications and mortality after surgery.¹¹⁶

Oxygen use in the elderly

With the increase in population ageing, anaesthetists are challenged to provide optima anaesthesia management for elderly patients with numerous co-morbidities. The recent scientific literature has suggested that this population requires special considerations when perioperative O₂ supplementation is provided. One of the hallmark changes that occurs with ageing is the altered transport, exchange, and utilization of O₂.¹¹⁷ Moreover, changes in the histological structure of the skin, with a decrease in the microcirculation, jeopardize wound healing in elderly patients.¹¹⁸ Hence, the possibility of perioperative O₂ supplementation in these patients should be considered from a broader viewpoint, taking into account the impact of ageing on the organism. Ageing has been demonstrated to be associated with significantly increased production and accumulation of ROMs and reduced antioxidant function, which can trigger various age-related disorders.^{119 120} As hyperoxia leads to enhanced production of ROMs, it is anticipated that perioperative use of high $F_{I_{O_2}}$ will potentiate disorders related to ageing, particularly those affecting the lungs and the brain.

Experimental evidence shows that the lungs in elderly subjects are more susceptible to hyperoxia during mechanical

ventilation.¹²¹ Increased production of ROMs, enhanced expression of pro-inflammatory cytokines,¹²² and irreversible structural changes with degeneration of elastic fibres in the lungs¹²³ all contribute to this finding. In addition to these adverse pulmonary effects, hyperoxia compromises the contractile function of the diaphragm in aged subjects.^{121 124} This disorder is related to hyperoxia-induced exacerbation of the generalized skeletal muscle destruction with age that takes place subsequent to myofibril injury.¹²⁵

The prevalence of chronic obstructive pulmonary disease (COPD) in the elderly is a major public health problem.¹²⁶ In view of accumulating evidence of the role of oxidative stress in the pathogenesis of COPD,¹²⁷ anaesthetic management of these patients demands special attention, with particular awareness of supplemental O₂ therapy. Even a modest increase in $F_{I_{O_2}}$ (<30%) for a short period (<1 h) leads to oxidative stress and airway inflammation in COPD patients.^{128 129} Another aspect of supplemental O₂ is related to the existence of lung areas with low V/Q ratio in COPD patients, ultimately manifested in a greater propensity to alveolar collapse when a high concentration of O₂ is administered.^{21 23} In contrast to these deleterious effects of intraoperative administration of O₂, O₂ can have a dual effect if administered before or after operation in patients with COPD. Accordingly, a recent study demonstrated that COPD patients benefit from a small increase in $F_{I_{O_2}}$ during preoperative cardiopulmonary exercise,

which results in an improvement in perioperative risk stratification.¹³⁰ Conversely, supplementation of a high concentration of O₂ after operation suppresses hypoxic drive, which is crucial in maintaining alveolar ventilation in the presence of COPD.¹³¹ Thus, in the patients at high risk of hypercapnia, O₂ should be carefully titrated in order to target O₂ saturation between 88 and 92%.¹³²

In the last decade, anaesthetists have become aware of the role of anaesthesia management in reducing postoperative cognitive dysfunction (POCD) in elderly patients.¹³³ Application of near-infrared spectroscopy in aged patients has revealed that adequate and optimal cerebral oxygenation is of paramount importance.^{133–135} However, supplementing O₂ pre-operatively leads to an increase in cerebral vascular resistance, with a subsequent decrease in CBF, independently of the effect of CO₂ on cerebral vasoreactivity.³⁹ This effect might be further enhanced by the impaired NO-mediated cerebral vasodilator response and the compromised CBF observed with ageing.¹³⁶ The resulting compromised cerebral desaturation not only may contribute to the higher incidence of POCD and longer hospitalization in elderly patients,¹³⁴ but also have long-term consequences on cognitive function. The findings from animal models have incriminated perioperative use of excessive O₂ in elderly subjects as one of the factors triggering development of Alzheimer's disease.^{137,138} Although the role of oxidative stress in the pathogenesis of Alzheimer's disease is also supported by clinical investigations,^{139–141} further studies are needed to establish the link between perioperative hyperoxia and various neurodegenerative disorders in aged humans.¹⁴²

Another concern in this population is related to a history of recent stroke and the potential for further neurological damage. As tissue hypoxia is linked to neuronal damage subsequent to stroke, compensation by supplementing high concentrations of O₂ is tempting. However, conflicting results have been reported from experimental and clinical studies. Experimental data demonstrated a worsening of brain injury and increasing mortality,^{143–144} whereas clinical investigations either failed to confirm the efficiency¹⁴⁵ or indicated only a transient improvement.¹⁴⁶ A recent multicentre cohort study concluded that hyperoxic ventilation of stroke patients worsens mortality, indicating the need for critical application of hyperoxia.¹⁴⁷

Conclusions and future perspectives

The predominant goal of the use of O₂ in the perioperative period is to provide adequate tissue oxygenation and thereby avoid the vicious spiral triggered by hypoxaemia. To address this challenge, anaesthesia management should consider O₂ supplementation as an important strategy to ensure optimal O₂ supply. The anaesthetist should be aware of the limitations of increasing the O₂ concentration in inspired gas situations with limited O₂ transport to the organs. Perioperative O₂ supplementation is one piece of the puzzle that involves optimization of O₂ delivery by the microcirculation. Automatic utilization of O₂ supplementation without a broad view of the needs of patient risks the development of hyperoxia-induced injury, which can enhance tissue damage particularly in patients

with pre-existing chronic disease or ischaemia-reperfusion injury. These features stress the importance of careful choice of O₂ delivery to patients to provide optimal tissue oxygenation and ensure a balance between hypoxia- and hyperoxia-induced harm. The tuning of the perioperative O₂ concentration should therefore take into account not only O₂ supply and consumption, but also age-specific aspects of O₂ demand and toxicity (Fig. 1). As O₂ demand and prevention of hypoxaemia are of critical importance, mainly during induction of and recovery from anaesthesia, a higher $F_{I_{O_2}}$ not exceeding 80% should be considered only in these critical phases (Fig. 2). Ageing affects the optimal O₂ concentration for maintenance of anaesthesia and in the post-operative period, where age-dependent O₂ saturation should be targeted (Fig. 2). Anaesthesia has benefited from technical advances, such as near-infrared spectroscopy, that facilitate the optimization of tissue oxygenation. The often neglected measurement of SvO₂ as a surrogate for balance between O₂ supply and demand deserves a more thorough consideration. Further research promises to advance our understanding of the effects of perioperative O₂ in a wide range of clinical situations, clarifying those areas where the findings currently remain conflicting.

Declaration of interest

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